A Dose Selection Phase 1 Study Evaluating the Safety and Tolerability of Silmitasertib (CX-4945) in Healthy Subjects

Protocol No.: CX4945-AV04-phase I

STATISTICAL ANALYSIS PLAN

Version: 1.0
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Biostatistician: Chen Tung

Confidentiality Statement

Approval of Statistical Analysis Plan
Protocol No : CX4945-AV04-phase I

The undersigned approved the SAP Version 1.0, dated 05-Jan-2023 as final.
Programming of the tables, figures and listings based upon the specifications within this document can proceed.

Senhwa Biosciences, Inc. Approval:

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Signature (CEO)	Print Name	**Date**

QPS-Qualitix Approval:

	Jo Chen	
Signature (Lead Statistician)	Print Name	**Date**

Please Note:
QPS-Qualitix will not notify Senhwa Biosciences, Inc. of minor modifications (e.g. modification of column or title) of tables, listings or figures that are different from SAP when generating data-driven tables, listings or figures after database lock.

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1. INTRODUCTION

This statistical analysis plan (SAP) is based on protocol CX4945-AV04-phase I Version 1.0 dated 30-August-2022 and protocol clarification letter #01 dated 27-December-2022. The SAP provides details of data handling procedures, statistical analysis methods for safety evaluations. It also outlines statistical programming specifications for tables and listings, and other details on the analyses not provided in the study protocol.

2. STUDY OBJECTIVE

Primary Objective

- To assess safety and tolerability of CX-4945 administered orally 200 mg QD, 200 mg BID and 400 mg BID for continuously 5 days to healthy subjects

Secondary Objectives

- To evaluate changes in blood chemistry and other health assessment

3. STUDY DESIGN

3.1 Summary of Study Design

This is a phase I single center, open-label, parallel design in 30 subjects to evaluate safety and tolerability of CX-4945 200 mg QD, 200 mg BID and 400 mg BID doses (10 subjects in each regimen) for continuously 5 days in healthy subjects for dose selection. Up to approximately 30 subjects will be enrolled into this study. A screening evaluation will occur within 28 days prior to Day 1. A subject screening number will be assigned to each subject in successive order of consent signing, beginning with S001. At the end of screening all qualified subjects will be assigned sequentially to following three treatment cohorts:

• Cohort 1: CX-4945 200 mg QD
• Cohort 2: CX-4945 200 mg BID
• Cohort 3: CX-4945 400 mg BID

A subject number will be assigned to participants when they have confirmed eligible for the study on Day 1. Each cohort will receive a unique numeric designation, and will precede the subject number (e.g. at cohort 1 the first two subjects would be 01-001 and 01-002; at cohort 2 the first two subjects would be 02-001 and 02-002). The total duration of the treatment will be 5 days. Subjects will be followed up at 14 days from the start of the treatment. The total duration for each subject in the study

(including the screening) will be up to 42 days.

3.2 Schedule of Activities

Table 1: Schedule of Activities

Procedure/Assessments	Screening Visit	Treatment				Follow-Up
Day	SV Day -28~ 0	Day 1 (Baseline)	Day 3	Day 5	Day 6 (EOT)	Day 14
Window Period		within 28 days after SV				±3 days
Informed Consent [1]	X					
Eligibility Evaluation [2]	X					
Subject Demographics	X					
Medical History [3]	X					
Physical Examination	X	X	X	X	X	X
Weight and Height	X					
Vital Signs [4]	X	X	X	X	X	X
ECG	X	X	X	X	X	
Laboratory Tests:	X	X	X	X	X	X
Hematology [5]	X	X	X	X	X	X
Blood Biochemistry [6]	X	X	X	X	X	X
Coagulation [7]	X	X	X	X	X	X
Serum/Urine Pregnancy Test [8]	X	X				X
Urinalysis [9]	X	X	X	X	X	X
Anti-HIV, Anti-HBV, Anti-HCV	X					
Anti-SARS-Cov2 [10]		X				
IP Administration		CX-4945 200 mg QD daily (Day 1 to Day5) CX-4945 200 mg BID daily (Day 1 to Day5) CX-4945 400 mg BID daily (Day 1 to Day5)				

Concomitant Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X

[1] Informed consent must be obtained prior to subject participation in any protocol-related activities that are not part of routine care.

[2] Initial evaluation of subject eligibility will be performed by Investigator. Subject number will be assigned on Day1 after confirming the subject eligibility.

[3] Medical history and current therapies (medications and non-medications).

[4] Vital signs will include blood pressure, heart rate, respiration rate, SpO2, and temperature.

[5] Hematology: Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total, differential count,(Absolute Neutrophil Count, Absolute Lymphocytes Count, Absolute Monocytes Count, Absolute Eosinophils Count, Absolute Basophils Count) and platelets.

[6] Blood biochemistry:

- Hepatic function indicators: total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, lactate dehydrogenase (LDH)
- Renal function indicators: BUN, Serum creatinine
- Electrolytes: sodium, potassium, chloride, magnesium, phosphorus, total calcium and bicarbonate,
- Other: Creatine phosphokinase (CPK), C-reactive protein (CRP), Creatine kinase-MB(CK-MB mass), Triglyceride, Total Cholesterol, Glucose AC, Uric Acid, γ-GT.

[7] Coagulation: Prothrombin time (PT) and International Normalized Ratio (INR)

[8] ONLY performed on women of childbearing potential. Pregnancy Test will be tested on screening, Day 1 prior dosing and Day 14.

[9] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.

[10] In response to the COVID-19 pandemic, the subject will need to follow the currently site's policies for COVID-19 to get the negative results of anti-SARS-Cov2 test before admission.

3.3 Endpoints

Primary Endpoint

To evaluate the adverse events occurring from Day 1 to Day 5 (including vital signs, physical findings, clinical laboratory, and electrocardiogram (ECG) results) as characterized by type, frequency, severity [as graded by the National Cancer Institute Common Terminology Criteria

for Adverse Events [CTCAE] version 5.0], timing, seriousness, and relationship to study therapy after administration of 200 mg QD, 200 mg BID and 400 mg BID for continuously 5 days to healthy subjects.

Secondary Endpoint

Changes in blood chemistry and other health assessments from Day 1, Day 3, Day 5, and Day 6 morning.

3.4 Data Monitoring Committee (DMC)

Throughout the trial, all safety and tolerability data will be reviewed and monitored by an independent DMC. The composition and functions of the DMC will be governed by a charter, which will be described elsewhere.

A DMC safety listing and table based on frozen cleaned data will be conducted by QPS-Qualitix. The DMC safety listing and table will be generated based on this SAP mock listing and table. (Refer to Appendix A and Appendix B)

4. GENERAL STATISTICAL ISSUES

In general, all summaries will be displayed by treatment group and overall, and if applicable. Unless otherwise noted, all summaries will be descriptive in nature and will include number of subjects (N) and number of events (E) if applicable.

4.1 Continuous endpoints

Descriptive statistics including number of observations, mean, median, standard deviation, minimum and maximum will be presented for the raw data as well as change from baseline. The mean and median will be presented with one more decimal than the original data; standard deviation will be presented with two more decimal than the original data; minimum and maximum values will be presented with the same precision as the original data. For the calculation of baseline corrected values, baseline is defined as the last information collected before dosing for each parameter.

4.2 Categorical endpoints

The count and percentages will be used to summarize the categorical data. Percentages with float will be presented with 2 decimals; percentages with divisible number will be presented with 0 decimal.

4.3 Sample size estimation

A total of 30 subjects will be assigned sequentially into 3 cohorts in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this proof-of-concept study.

5. DATA HANDLING PROCEDURES

5.1 Coding System

Medical coding includes AE coding, medical history coding and concomitant medication coding. AE coding and medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or higher and concomitant medication will be coded by WHODrug Global, B3, September 2022 or the most updated version. The latest version before database lock (DBL) will be adopted for final analysis.

5.2 Missing Data Handling

For data listings, all raw data will be reported/ displayed exactly as provided. No imputation will be performed on missing data. All analyses will be performed on data available at the time point considered. In summary tables, the number of subjects without missing data will be presented unless otherwise specified. In calculations of percentages, subjects with missing data will not be considered in numerator of denominator unless otherwise specified.

6. ANALYSIS OF STUDY POPULATIONS

Intent-to-treat (ITT) Population

The ITT population is defined as all assigned subjects who received at least one dose of study drug. This population will be used as the primary analysis population for analysis of the primary and secondary endpoints.

Per-protocol (PP) Population

The PP population is defined as the set of subjects who meet the ITT population requirements and are not associated with any major protocol violations. This population will be identified before the database lock. This population will be used as the supportive analysis population for analysis of the primary and secondary endpoints.

Safety Population

The Safety population is defined as any subject receiving at least one dose of CX-4945. This population will be used for the analysis of safety parameters.

Because of primary/secondary endpoint equals to safety endpoint. If the subjects included in three populations are the same, all analysis tables will only be presented by safety population with a footnote explaining that all populations are the same. Otherwise, it will be analyzed by three populations.

7. DISPOSITION OF PATIENTS AND STUDY COMPLETION

Data on date of visit will be listed in Listing 16.2.1.1. Data on the completion status and primary reason for study discontinuation will be listed in Listing 16.2.1.2. The subject disposition and completion status will be summarized by treatment group in Table 14.1.1. The subject eligibility will be listed in Listing 16.2.1.3. All minor and major protocol deviation(s) will be listed in Listing 16.2.2. All subjects who excluded from ITT, PP and safety population will be listed in Listing 16.2.3.

8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 Demographics and Baseline Characteristics

Subject demographics will be listed in Listing 16.2.4.1. Subject height, weight and body mass index (BMI) collected at screening will be listed in Listing 16.2.4.7. Demographics and baseline characteristics including height, weight, BMI, medical history, prior and concomitant medications/therapies will be analyzed with descriptive statistics and summarized for ITT, PP and safety population by treatment group in Table 14.1.2.

8.2 Medical History

Medical history will be coded by MedDRA version 25.1 or higher and listed by subject in Listing 16.2.4.2.

8.3 Concomitant Medication

All concomitant medications will be coded by WHODrug Global, B3, September 2022 or the most updated version and listed in Listing 16.2.4.3 and be summarized by treatment group using the coded term and preferred name in Table 14.1.3. Concomitant non-medication therapies will be listed in Listing 16.2.4.4.

8.4 Anti-SARS-Cov2

Subject anti-SARS-Cov2 test collected on Day 1 will be listed in Listing 16.2.4.5.

8.5 Serology

Clinical laboratory analyses serology test collected at Screening will be listed in Listing 16.2.4.6.

9. EXTENT OF EXPOSURE AND DRUG COMPLIANCE

9.1 Study Drug Administration

The information of date and time of study drug administration will be listed in Listing 16.2.5.

10.SAFETY ANALYSIS

10.1 Adverse Events

All AEs recorded in the eCRF (electronic Case Report Form) will be coded using the MedDRA 25.1 or higher and listed in Listing 16.2.7.

AE study day and duration will be added in the AE listings. The following calculations and derivations will be used, making the most conservative judgment.

- For study day of AE as "XX" or "Prior":
- Study day = AE onset date - date of prior administration + 1.
- If AE onset date is prior to date of first administration, then the study day will be "Prior".
- If onset date is unknown, study day will be missing.

- For duration of AE as "XXDXXHXXM":
- Duration = resolution date and time of the event minus onset date and time of the event.
- If onset or resolution time unknown, then the duration will be calculated based on resolution date and onset date only, and plus 1.
- If onset or resolution date is unknown, duration will be missing.

Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment.

As defined in the eCRF, all AEs will be assigned a severity of: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe or medically significant but not immediately life-threatening), Grade 4 (Life-threatening consequences) or Grade 5 (Death related to AE). All AEs will be classified as either

related or unrelated to study drug. A study drug-related AE is defined as any TEAE that is assessed to have 'Possibly Related', 'Probably Related' or 'Definitely Related' relationship to study drug. An AE not related to study drug is defined as any AE that is assessed as 'Unrelated' or 'Unlikely Related' to study drug.

Frequency counts will be tabulated and displayed by the MedDRA primary system organ class (SOC) and preferred term (PT) by group and overall.

A general summary of all TEAEs and serious TEAEs will be provided in Table 14.3.1.1. This summary will present the event numbers, subject numbers, and subject percentages according to the following categories:

- Subject with Any TEAE
- Subject with Any TESAE
- Subject with Any Drug-Related TEAE
- Severity
- Was This a SAE?
- Action Taken with Study Drug
- Treatment Required
- Relationship to Study Drug
- Outcome

Other summary tables for TEAEs will include:

- Table 14.3.1.2: Treatment-Emergent Adverse Events - MedDRA
- Table 14.3.1.3: Treatment-Emergent Adverse Events - MedDRA (Preferred Term over XX % in Any Treatment Group)
- Table 14.3.1.4: Treatment-Emergent Adverse Events by Severity - MedDRA
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- Table 14.3.2.1: Listing of Subjects with Treatment-Emergent Serious Adverse Events

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- Table 14.3.2.3: Listing of Subjects with Treatment-Emergent Adverse Events Leading to Death

10.2 Clinical Laboratory Tests

Clinical laboratory analyses including hematology, blood biochemistry, urinalysis, microscopic exam, coagulation and serum/urine pregnancy test will be listed in Listing 16.2.8.1 through Listing 16.2.8.6.

All abnormal laboratory values and evaluation flags 'NCS' (not clinically significant) or 'CS' (clinically significant) will be listed in Table 14.3.4.

The observed results and the mean change from baseline of hematology, blood biochemistry, urinalysis and coagulation will be summarized by each testing parameter, each visit and group in Table 14.3.5.1 through Table 14.3.5.4. The shift tables of hematology, blood biochemistry and urinalysis will be provided by each testing parameter, post baseline visit and group in Table 14.3.5.5 through Table 14.3.5.8.

For any laboratory results reported as "<limit of quantification (<LLOQ)", the numeric value used for summary will be the half of LOQ value. For results reported as ">limit of quantification (>ULOQ)", the numeric value used for summary will be the LOQ value plus one unit of the minimum digits of the parameter. For example, if the results is "> 2", the numeric value will be 2 plus 1 which is 3; if the results is "< 0.5", the numeric value will be half of 0.5 which is 0.25.

10.3 Vital Signs

Vital signs will be listed in Listing 16.4.1. The observed vital signs and the mean change from baseline over each visit will be analyzed with descriptive statistics and summarized by group in Table 14.3.6.

10.4 12-Lead Electrocardiogram (ECG)

12-lead ECG will be listed in Listing 16.4.2. The observed 12-lead ECG and the mean change from baseline over each visit will be analyzed with descriptive statistics and summarized by group in Table 14.3.7.

10.5 Physical Examination

Physical examination will be listed in Listing 16.4.3. The counts and percentage of physical examination will be summary by group in Table 14.3.8.

11. COMPUTER METHODS

All statistical analyses will be conducted using SAS® software, Version 9.4 of the SAS System for Windows 10. Copyright© 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

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